REVIEW ARTICLE

Multidrug Resistant Acinetobacter in Patient with Ventilator Associated Pneumonia: Review Article

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Abstract:

Acinetobacter is a complex genus, with multiple species. Acinetobacter species are the common etiology of nosocomial infections, principally nosocomial pneumonia catheter-associated bacteremia and urinary tract infections. Multidrug Resistant (MDR) Ventilator Associated Pneumonia (VAP) by Acinetobacter spp is increasingly reported from different parts of the world. Transmission of Acinetobacter is aid by the organism's environmental stubbornness, resistance to desiccation and evasion of host immunity. The virulence properties demonstrated by Acinetobacter spp. is primarily by evasion of rapid clearance by the immune system. The capsular polysaccharide is a critical virulence factor that enables immune evasion and lipopolysaccharide triggers septic shock. Conversely, the primary factor of clinical outcome is antibiotic resistance. Acinetobacter spp. has become a discreditable threat for patients on mechanical ventilation. Considering high rate of antibiotic resistance, new preventive and therapeutic alternative approach for MDR Acinetobacter spp. infections are urgently needed. Worldwide drug resistance in Acinetobacter baumannii is growing. This review article is emphasised on incidence of VAP due to MDR Acinetobacter, phenotypes, genotypes, associated risk factors and preventive strategy.

Keywords: Acinetobacter spp, Ventilator Associated Pneumonia, Mechanical Ventilation, Multidrug Resistant, Phenotypes, Genotypes

Introduction:

The species Acinetobacter baumannii (A. baumannii) was largely unknown 30 years ago. Acinetobacter species (spp) are Gram-negative bacteria that have become one of the most difficult pathogens to treat. It is now a predominant pathogen in many hospitals as it has acquired resistance genes to virtually all antibiotics capable of treating Gram negative bacteria, including the fluoroquinolones and the cephalosporins. Over a decade, nosocomial infections due to A. baumannii have increased towards Multidrug Resistance (MDR), mostly in intensive care units with patients on ventilator. A. baumannii is a rapidly emerging nosocomial pathogen and causes severe infections that include bacteraemia, pneumonia, meningitis, urinary tract and wound infections. It has now become a major cause of nosocomial infection worldwide due to its notable inclination to swiftly acquire resistance to a wide range of antibacterial agents [1]. Ventilator-associated Pneumonia (VAP) is one of the most common Intensive Care Unit (ICU) acquired infection (6 to 52%) and a major cause of morbidity, mortality and increased financial load in ICUs. The overall rate of VAP is higher in developing countries (13.6) ICUs than quoted from the US (3.3 per 1000 ventilator-days). Despite of low virulence, A. baumannii has emerged as MDR pathogen responsible for hospital acquired infections that are difficult to control and treat. A. baumannii has natural MDR phenotype, its capability of acquiring new
mechanisms of resistance. Recently genome sequencing of several *A. baumannii* isolates, has led to the discovery of the extraordinary plasticity of their genomes, which is linked to their great proclivity to adapt to any environment [2]. In India, VAP caused by MDR-*Acinetobacter baumannii* (MDR-AB) isolates are associated with significant mortality, morbidity and costs. MDR-AB infections are difficult to treat owing to the extremely limited treatment options [3, 4]. Current knowledge about *A. baumannii*, including phenotypes, genotype, epidemiological aspects and resistance to antibiotics, are reviewed in this article. The present review reports the incidence of VAP, incidence of MDR VAP due to *A. baumannii*, risk factors for developing MDR-VAP due to *A. baumannii* and preventive strategy for MDR in the different parts of world have been discussed.

Rationale of review:
Multidrug resistant among *Acinetobacter* infection is associated with a high mortality rate and limits the therapeutic options. During the past few decades, *Acinetobacter* has emerged as an important nosocomial pathogen, affecting patients in the ICU setting, globally. *A. baumannii* has been recognised as a leading cause of VAP in various parts of the world. VAP remain important causes of morbidity, mortality and financial burden. Increasing antimicrobial resistance has stir up the concern of the failure of antibiotic treatment. VAP due to MDR *Acinetobacter* has different phenotypes, genotypes, antibiotic resistance pattern and associated risk factors for developing VAP, across the world. We performed a review of MDR-VAP due to *A. baumannii*.

Database searches and study selection:
Studies included in this review are, cross-sectional, case-control, cohort studies and systemic review. The relevant studies were identified from searches of the PubMed, Medline, Embase and Scopus databases (using keywords: *A. baumannii*, MDR-Ventilator associated pneumonia, phenotype, and genotype of MDR -*A. baumannii*). All studies included in this review were monitored for the development of VAP using clinical and microbiological criteria, until discharge or death. The diagnosis of VAP was established on the basis of clinical and radiological parameters as per Centre of Disease Centres (CDC) Guidelines [5].

Diagnostic criteria and case definition for VAP:
VAP is defined as a pneumonia occurring 48 h or more after endotracheal intubation, with new and/or progressive radiological infiltrate, and at least two of the following features:

A. **Radiology:**
   - Two or more serial chest radiographs with at least one of the following:
     - New or progressive and persistent infiltrate consolidation, cavitations

B. **Signs, symptoms and laboratory**
   For any patient, at least one of the following:
   - Fever (>38°C or >100.4°F) with no other recognized cause
   - Leucopenia (<4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm3)
   - For adults >70 years old, altered mental status with no other recognized cause and at least two of the following
     1. New onset of purulent sputum or change in character of sputum or increased respiratory secretions, or increased suctioning requirements
     2. New onset or worsening cough or dyspnoea or tachypnea
3. Rales or bronchial breath sounds
4. Worsening gas exchange $\text{PaO}_2/\text{FiO}_2 < 240$
   (increased oxygen requirements or increased ventilator demand)

- **The Clinical Pulmonary Infection Score (CIP):**
  (CPIS) is based on six clinical assessments, for patients clinically suspected of VAP on the day of endotracheal secretions collection, (CPIS with score $\geq 6$).
  Positive quantitative culture of the EA (count $\geq 10^6$ CFU/mL)
  MDR pathogens were defined as resistant to three or more classes of antibiotics.

- **Early-onset VAP:**
  Patients developing VAP within the first four days of Mechanical Ventilation (MV) were classified as having early onset VAP

- **Late-onset VAP:**
  Patients developing VAP five or more days after the initiation of MV were classified as having late onset VAP

**Microbiological methods:**
Susceptibility to different classes of antibiotics was determined by the Kirby Bauer disc diffusion method and interpreted. [Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Susceptibility Testing] Phenotypic and genotypic resistance to $\beta$-lactamases was determined using standard methods [6]. Combination disk method, modified Hodge test, EDTA disk synergy test and AmpC disk test were performed for detection of Extended Spectrum $\beta$-lactamases (ESBL), carbapenemases, Metallo-$\beta$-lactamases (MBL) and AmpC $\beta$-lactamases respectively in various studies. $\text{blaOXA-23, blaOXA-24, blaOXA-51, blaTEM, blaSHV, blaCTX-M,}$
and $\text{blaPER} \beta$-lactamase genes were searched by Polymerase Chain Reaction (PCR) and sequencing. Pulsed-field gel electrophoresis for genotyping and antimicrobial susceptibility testing for clinically relevant antimicrobials were performed in these studies [7]. Resistance determinants were characterized by using different phenotypic (accumulation assay for efflux) and genotypic (PCR, DNA sequencing, plasmid analysis and electrophoresis) analyses by various studies according to protocol.

**Characteristics of *Acinetobacter* spp:**
Gram-negative coccobacilli that were likely "Acinetobacter" were isolated as early as 1914 and repeatedly through the 1940s but were previously referred to as Mimapolyomorphia (now *Acinetobacter lwofii*), Herelleavaginicola (now *A. baumannii* or *A. calcoaceticus*), *Bacterium anitratum*, B5W, and *Moraxella lwofii* [1]. *A. baumannii* is a ubiquitous, non-fermenting, aerobic Gram-negative bacterium with intrinsic resistance to multiple antimicrobial drugs [2]. The genus, *Acinetobacter*, as has been currently defined, comprises Gram-negative, strictly aerobic, non-fermenting, non-fastidious, non-motile, catalase-positive, oxidase-negative, coccobacilli and opportunistic bacteria. *A. baumannii* is an encapsulated containing proteins, namely porins and efflux channels, on the outer cell membrane, which mainly contribute to their resistance mechanisms. This genus has undergone significant taxonomic modifications over the last 30 years. Compared to other Gram negative bacteria, it has fewer and smaller porin channels, which thereby decrease its cell permeability and increase its antibiotic resistance. The cell wall of the bacteria changes according to the environmental conditions.
conditions, thus causing an increase in its thickness when it is placed in a very dry conditions, thereby again providing extra resistance at high temperatures and dormant conditions. *A. baumannii* is generally considered as opportunistic infections and can be non-pathogenic in healthy individuals [8]. *A. baumannii* is one of the most important nosocomial pathogens because of its longevity in the hospital environment and ability to resist various antimicrobial agents and to colonize susceptible patients treated with broad-spectrum antibiotic [9].

**Biology, virulence factors, risk factors for Drug resistance in Acinetobacter spp:**

*Acinetobacter* was described by a Dutch microbiologist a century ago, as *Micrococcus calcoaceticus* known as *Acinetobacter* in 1950's and more than 25 species have been identified. Most of the cases are usually seen in the ICUs of hospitals, in patients with deprived immunity and in those who are on various invasive equipments, like ventilator machines and catheters. The irrational use of antibiotics in the ICU set up and the various bacterial mechanisms of resistance contribute to summation of resistance function for this untreatable, risky microorganism. Risk factors for colonization or infection with multidrug-resistant *A. baumannii* are prolonged length of hospital stay, exposure to an ICU, mechanical ventilation, prolonged exposure to antimicrobial agents, surgical and invasive procedures, and severe illnesses or comorbidites. Presence of the porin channels, efflux mechanisms and the non static behaviour of the bacteria in hot and humid conditions lead to extensive antimicrobial resistance. There is rising concern about antimicrobial resistance among *Acinetobacter* spp since the past decade [10].

The virulence factor like Porin (OmpA, Omp33-36, Omp22, CarO, OprD-like) are involved in adherence and invasion, induction of apoptosis, serum resistance, biofilm formation. Capsular Polysaccharides are required for growth in serum, survival in tissue infection, biofilm formation. Capsular Lipopolysaccharides (LPS) and Phospholipase (PLC and PLD) are responsible for Growth in serum, survival in tissue infection, biofilm formation, serum resistance, invasion, in vivo survival. Outer Membrane Vesicle (OMV) is involved in delivery of virulence factors, horizontal transfer of antibiotic resistance gene. *A. baumannii* NfuA Fe-S scaffold protein, that participates in the formation of Fe-S clusters and plays a role in cell responses to iron chelation and oxidative stress, has also been identified as a virulence factor. Several protein secretion systems have been identified in *A. baumannii*. The most recently described *A. baumannii* secretion system is a Type II Secretion System (T2SS). β-lactamase PER-1 has been suggested to be an *A. baumannii* virulence factor. PER-1 is an ESBL, but this gene is associated with cell adhesion. CipA-binding plasminogen is converted to active plasmin that degrades fibrinogen and complement C3b, which contributes to serum resistance of *A. baumannii*.

**Antimicrobial resistance of A. baumannii**

1. Beta-Lactamases (VIM/IMP):

   Inactivation of β-lactams by β-lactamases is a major antibiotic resistance mechanism in *A. baumannii*. Based on sequence homology, β-lactamases are grouped into molecular classes, A, B, C and D (β-lactamase genes: *bla*OXA-23, *bla*OXA-24, *bla*OXA-58, *bla*OXA-51, *bla*TEM, *bla*SHV, *bla*CTX-M, and *bla*PER)
2. Efflux Pumps:
Efflux pumps are associated with resistance against many different classes of antibiotics, such as imipenem and tigecycline, in *A. baumannii*. The TetB efflux pump is the main determinants of minocycline resistance.

3. Permeability Defects:
A change in envelope permeability can influence antibiotic resistance. For example, porins form channels that allow transport of molecules across the outer membrane.

4. Aminoglycoside - Modifying Enzymes:
Aminoglycoside-modifying enzymes are the major mechanism by which *A. baumannii* confers resistance to aminoglycosides.

5. Alteration of Target Sites:
Modifications in antibiotic target sites for antibiotics can induce antibiotic resistance in *A. baumannii*. In the absence of other known resistance mechanisms, only overexpression of altered PBPs with a low affinity for imipenem induces imipenem/carbapenems resistance.

6. AdeABC is associated with decreased susceptibility to tigecycline. Quinolone resistance is associated with modifications in GyrA (one subunit of DNA gyrase)

7. Change in affinity for binding was seen in case of colistin resistance

8. The changes in the membrane binding and changes in bacterial targets due to point mutations in gyrA and parC topoisomerase enzymes confer resistance against quinolones

**MDR-AB:**
MDR-AB is defined as an *A. baumannii* strain resistant to at least three different groups, penicillins and cephalosporins (including inhibitor combinations), fluoroquinolones and aminoglycosides, has emerged and has been reported worldwide to significantly increase the morbidity, mortality, and cost of treatment. The incidence of MDR-AB is increasing worldwide. *Acinetobacter* spp exhibit multidrug resistance through production of β-lactamases, alterations in Outer Membrane Proteins (OMPs) and Penicillin-Binding Proteins (PBPs) and increased activity of efflux pumps. Resistance to β-lactams appears to be primarily caused by production of β-lactamases which include ESBLs, MBLs and oxacillinases. MBLs are classes of powerful enzymes called carbapenemases responsible for antibiotic resistance. Four groups of these enzymes have been described in *A. baumannii*, including IMP-like, SIM-1, NDM-type, and VIM-like carbapenemases. MBLs-encoding genes are located on integrons that can be transmitted from one bacterial species to another. ESBLs are encoded by TEM-type, SHV-type, and CTX-M-type genes; they are resistance to penicillins and third-generation cephalosporins. The drug of choice to treat nosocomial infection caused by MDR-AB is the carbapenems. However, there is an increasing rate of carbapenem-resistant *A. baumannii* around the world. *Acinetobacter* species are distinguished for their intrinsic resistance to antibiotics and for their ability to acquire genes encoding resistance determinants like, production of β-lactamases, aminoglycoside-modifying enzymes, diminished expression of outer membrane proteins, mutations in topoisomerases, and up-regulation of efflux pumps play an important part in antibiotic resistance. The accumulation of multiple mechanisms of resistance leads to the development of multiply resistant or even "panresistant" strains [11]. *A. baumannii* is labeled as MDR-AB when it
is resistant to more than two of the five classes of antibiotics [cephalosporins (ceftazidime or cefepime), carbapenems (imipenem or meropenem), Ampicillin/sulbactam, Fluoroquinolones (ciprofloxacin or levofloxacin) and Aminoglycosides (gentamicin, tobramycin, or amikacin)]. Carbapenems were considered as the most important agents for the treatment of infections caused by MDR-AB. Carbapenem Resistant *A. baumannii* (CRAB) is now emerging as a potential threat and it is usually resistant to almost all antimicrobial classes except colistin and tigecycline. The most important mechanism of CRAB is enzyme inactivation by the production of β-lactamases, which hydrolyze the carbapenams. These hydrolyzing enzymes include MBL and class D β-lactamases (widespread). The main gene clusters responsible for this resistance are *bla*OXA-23-, *bla*OXA-24/40- and *bla*OXA-58-like gene clusters, identified either in the chromosome or in plasmids of *A. baumannii* strains [8]. Colistin is the last resort for treatment of multidrug-resistant *A. baumannii*. Unfortunately, resistance to colistin has been reported all over the world. The highest resistance rate was reported in Asia, followed by Europe. The mechanism of resistance might be loss of lipopolysaccharide or/and the PmrAB two-component system [12].

**Genotype and phenotype of MDR A. baumannii in patients with VAP:**

Different genotypes and phenotypes were reported by various studies from India and overseas. Royer *et al* reported all CRAB carbapenem isolates of *A. baumannii* were OXA-23 producers [Molecular typing: clone A (clinical) and H (surface)] [13]. Baker *et al*. reported production of carbapenemases MBLs in *Acinetobacter* (blaVIM2) [14]. Patro *et al.* and Khelgi *et al.* quoted AmpC β-lactamase and MBL was positive MDR-AB with VAP [7, 15]. Joseph *et al* and Khurana *et al.* noted ESBL, AmpC and carbapenemase genes in their study of MDR *Acinetobacter* spp [16, 6]. Banerjee *et al.* (2018) reported significant patients with Hospital Acquired Pneumonia (HAP) with MDR *Acinetobacter* spp. with imipenem resistance in majority of isolates (*bla*IMPA, *bla*VIM, *bla*NDM-1 and *bla*OXA-23-like genes) [17]. Ghada *et al.* observed carbapenem resistant isolates were positive for *bla*OXA-51-like gene, *bla*OXA-23 like gene, *bla*OXA-58 among MDR isolates of *Acinetobacter* [18]. Dey *et al.* reported AmpC β-lactamases and MBLs producing *Acinetobacter* isolates in their study [19]. Thakuria *et al.* (2013) and De *et al.* (2018) concluded that there was carbapenemase producers showed high degree of cross resistance to antibiotics (46%) in their cohort [20, 21]. Goel *et al.* (2012) found presence of MBLs in 62.96% of *A. baumannii* isolates [22]. Karampatakis *et al.* (2017) reported carbapenem-resistant (CR) strains with VIM and OXA-23 carbapenemases [23]. Singh *et al.* in their study stated that, the gene clusters responsible for this resistance were *bla*OXA-23-, *bla*OXA-24/40 and *bla*OXA-58-like gene clusters [8]. Srinivasan *et al.* observed presence of *bla*OXA-23 and ISAb1 linked *bla*OXA-66 in *Acinetobacter* spp. with imipenem resistance. MDR had *bla*ADC-26, class 1 integron-borne aminoglycoside modifying enzymes and sense mutations in *gyrA*/*parC* and active efflux (*adeB* efflux gene) [24]. Fatma *et al.* reported meropenem resistance was associated with AmpC β-lactamase, MBLs and Efflux pump *Acinetobacter* isolates. Ramoul *et al.* reported *bla*OXA-51, *bla*OXA-23 and *bla*TEM-1 gene in their *Acinetobacter* isolates [4]. Ganjo *et al.* quoted *A. baumannii* with *bla*OXA-23-like and *bla*OXA-24-like gene with majority of *bla*OXA-23-like isolates had the
ISAba1 insertion sequence which is responsible for carbapenem resistance [25]. Mohammad et al. reported presence of types A, B, C, D, E, tet A and tet B genes in their study of A. baumannii isolates [26]. European clones I to III, carbapenem-resistant genotypes and novel international clone was quoted by Petersen et al. [27]. Production of class D OXA carbapenemases and class B MBL plays a predominant role in contributing to carbapenem resistance to A. baumannii worldwide (Fig. 1).

**Prevalence of MDR-** Acinetobacter VAP:**
Various factors affect the incidence of MDR VAP due to A spp. including, criteria, ICU protocols, implementation of VAP bundle, ICU setting and antimicrobial policy. The rate of MDR VAP due to A. baumannii is more in developing countries as compared to western world and developing country. [28, 15, 6, 17, 29, 31, 32, 4, 14, 26, 33, 18, 34, 21, 19, 35, 7, 25, 36, 37, 38] (Fig. 2).
Drugs Resistance Pattern of MDR-AB in VAP:

*A. baumannii* is an opportunistic pathogen with increasing clinical significance, particularly in intensive care patients, causing nosocomial infections including VAP. The organism has the potential to persist in hospital milieu for many days. Many *Acinetobacter* spp are resistant to frequently used antibiotics like aminopenicillins, ureidopenicillins, cephalosporins and aminoglycosides. Carbapenems, β-lactam/β-lactamase inhibitor combinations and tetracyclines like minocycline and tigecycline and colistin are the commonly used against severe *A. baumannii* infections. Fatma *et al* (2014) (Egypt) reported 75% of MDR-AB isolates. *A. baumannii* exhibited high resistance rate to imipenem (66.6%), meropenem (73.3%) and cefazolin and cephalothin (100%) with moderate susceptibility to tetracycline (40%) and gentamicin (33.3%). Total 44.4% *A. baumannii* were positive for AmpC β-lactamase and 55.6% for MBLs. The efflux pump was detected in 77.8% of isolates [4]. Srinivasan *et al*. (2009) quoted MDR-AB in 79.5% with (*bla*OXA-23 in 13% and ISAba1 linked *bla*OXA-66 in 79.5%) isolates with high level imipenem resistance. The OXA producing isolates, had multidrug resistance by *bla*ADC-25, class I integron-borne aminoglycoside modifying enzymes, presence of sense mutations in *gyrA/parC* and involvement of active efflux (with evidence for the presence of *adeB* efflux gene) [24]. Karampatakis *et al*. (2017) reported Carbapenem-resistant (CR) strains, VIM and OXA-23 carbapenemases among *A. baumannii* [23]. Royer *et al*. (2015) (Brazil) reported that, the
VAP caused by carbapenem resistant *A. baumannii* (OXA-23) [13]. Ramoul et al. (2013) reported that, the *A. baumannii* are resistant to all β-lactams (*bla*OXA-51 gene, *bla*OXA-23 and *bla*TEM-1 [39]. Mohammad et al. (2014) Iran quoted, 89% of *A. baumannii* were resistant to tetracycline 35% to Minocycline 25% to doxycycline and were sensitive to tigecycline [tet B (87.6%) and tet A (2.2%) genes and coexistence of tet A and tet B (1.1%)]. Distribution of REP-types among *A. baumannii* isolates was types A (40%), B (30%), C (10%), D (5%) and E (5%). They concluded that, *tet A* and *tet B* genes play an important role in the induction of resistance for tetracyclines [26].

The various studies have reported the drug resistance to Carbapenem, β-lactam and Tetracycline for *A. baumannii* [13, 14, 6, 17, 16, 36, 40, 38, 18, 19, 20, 31, 41, 4, 25, 26]. We compared the various studies in reference to incidence, risk factors, genotype, phenotype, drug resistance pattern, preventive strategy of MDR-Acinetobacter associated ventilator associated pneumonia in different parts of the world (Table 1).

### Table 1: Comparison Prevalence, Risk Factors, Genotypes of MDR Acinetobacter Associated with VAP

<table>
<thead>
<tr>
<th>References</th>
<th>Type of study</th>
<th>Patients (n)</th>
<th>Prevalence of VAP &amp; MDR-Ab</th>
<th>Risk factors for VAP</th>
<th>Phenotype and genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Cohort of (14 months)</td>
<td></td>
<td>carbapenem resistant <em>Ab</em>.</td>
<td>Trauma and inappropriate antimicrobial therapy</td>
<td>All carbapenem resistant were OXA-23 producers; Molecular typing: clone A (clinical) and H (surface)</td>
</tr>
<tr>
<td>14</td>
<td>Prospective</td>
<td>117</td>
<td>66.7% resistant to imipenem (MBL producers)</td>
<td>Production of carbapenemases, especially MBLs. <em>Acinetobacter</em> isolates were highly resistant: 80.8%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cross-sectional study</td>
<td>100</td>
<td>The prevalence of VAP was 35% MDR: 60.87%</td>
<td><em>Acinetobacter</em> spp. 10 (31.25%), AmpC β-lactamase: 35.29%, MBL: 17.64%. <em>Acinetobacter</em> spp. showed 100% resistance to ceftazidime, amikacin and ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Retrospective</td>
<td>n=108</td>
<td>MDR: 70%</td>
<td>Risk factors: Duration of intubation and inappropriate antibiotics; Crude mortality rate was over 70%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>120</td>
<td>VAP with MDR pathogens (Ab) ssp: 37.83%</td>
<td>MBL AmpC β-lactamases</td>
<td>MBL was produced by 44.44% of <em>Acinetobacter</em> spp and AmpC β-lactamases 71.43%</td>
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<tr>
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<tr>
<td>6</td>
<td>5-year period</td>
<td></td>
<td>$A. baumannii$ (54%)</td>
<td>A high rate of MDR ESBL, AmpC and carbapenemase genes</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Prospective (15 months)</td>
<td></td>
<td></td>
<td>Acinetobacter spp: late-onset VAP</td>
<td>Production of ESBL, AmpC β-lactamases and MBL</td>
</tr>
<tr>
<td>17</td>
<td>A laboratory-based audit 5 years</td>
<td>993 cases (100) isolates of Ab.</td>
<td>88.02% MDR and 61.97% XDR</td>
<td>Longer duration of hospital stay: 88.02% MDR and 61.97% XDR</td>
<td>VAP resistant to imipenem and 88.02% MDR and 61.97% XDR. ($bla_{IMP}$ (89%), $bla_{VIM}$ (51%), $bla_{NDM-1}$ (34%), &amp; $bla_{OXA-23-like}$ (93%) genes)</td>
</tr>
<tr>
<td>18</td>
<td>Descriptive, cross-sectional</td>
<td>44</td>
<td>$A. baumannii$ isolates (100%) were (MDR).</td>
<td>Age&gt;40, Length of hospital stay, Prior use of antibiotics</td>
<td>Carbapenems resistant isolates: $bla_{OXA-51-like}$ gene, $bla_{OXA-23}$ like gene, $bla_{OXA-58}$, Colistin sensitivity: 93.2%</td>
</tr>
<tr>
<td>19</td>
<td>Prospective</td>
<td>97</td>
<td>VAP: 45.4% and MDR Ab: (47.9%)</td>
<td>Stress-ulcer prophylaxis, use of antibiotics, Re-intubation</td>
<td>30.43% $Acinetobacter$ spp : AmpC β-lactamases and MBLs: 21.74%</td>
</tr>
<tr>
<td>21</td>
<td>Cross-sectional</td>
<td>130</td>
<td>VAP: 40.8%, late-onset VAP: 81.13%</td>
<td>Diabetes mellitus, advancing age (&gt;60 yrs), COPD</td>
<td>$Acinetobacter$ spp:33.96% Carbapenem resistance: 46% MDR-Ab: 70.37%</td>
</tr>
<tr>
<td>29</td>
<td>Retrospective</td>
<td>43 (two-year)</td>
<td>$Ab$: 41.8%</td>
<td>Resistant antibiotype, MV</td>
<td>Most of $A. baumannii$ isolates were MDR.</td>
</tr>
<tr>
<td>20</td>
<td>Prospective one year</td>
<td>100</td>
<td>$A. baumannii$: 7.55%</td>
<td></td>
<td>Carbapenemase producers showed cross resistance</td>
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<tr>
<td>42</td>
<td>Retrospective</td>
<td>134</td>
<td>$Acinetobacter$ spp. (60%)</td>
<td></td>
<td>Mortality : 46%</td>
</tr>
<tr>
<td>31</td>
<td>Prospective</td>
<td>60</td>
<td>head injury, cerebral hemorrhage and COPD</td>
<td></td>
<td>MDR-AB VAP cases: 11.6%</td>
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<tr>
<td>References</td>
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<tr>
<td>40</td>
<td>Prospective</td>
<td></td>
<td>VAP was 42.5% MDR-AB: 66.7%</td>
<td>GNB:78.6%</td>
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<td><em>A. baumannii</em>: 32.1%</td>
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<tr>
<td>30</td>
<td>Prospective</td>
<td>95</td>
<td>40.1 VAP infections/1000</td>
<td>Longer ICU stay</td>
<td><em>Acinetobacter</em> species: 53.2% MDR:27.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elderly patients</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Prospective</td>
<td></td>
<td>VAP 4.1-25.3/1000 Days</td>
<td></td>
<td><em>A. baumannii</em>: 100%. MDR:55%-76%</td>
</tr>
<tr>
<td>34</td>
<td>Retrospective</td>
<td>132</td>
<td>MDR 72.7%</td>
<td>Increased ICU stay and longer intubation time</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Cross-sectional</td>
<td>100 patients</td>
<td>VAP: 44.2% Ab: .18%</td>
<td>Age, COPD, DM, MOF, duration of MV</td>
<td><em>Acinetobacter</em> spp were the most resistant pathogens</td>
</tr>
<tr>
<td>44</td>
<td>Retrospective</td>
<td>54</td>
<td>Male, high APACHE II score, renal failure and low platelet</td>
<td>Mortality was developed in 70%.</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Prospective</td>
<td>202</td>
<td>VAP: 14.85% (23.2 VAP/1000 VD)</td>
<td>Reintubation and tracheostomy prolonged duration of mechanical ventilation, ICU stay associated with MDR-AB (48.21%)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Prospective</td>
<td>53</td>
<td>MDR-AB 49.09%</td>
<td>MBLs: 62.96%</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Prospective</td>
<td>140 patients</td>
<td>VAP was 21.875 per 1,000 ventilator days.</td>
<td>Prior antibiotic therapy, hospitalization and MV, supine head position, reintubation unconsciousness</td>
<td>late onset VAP: 60.7% <em>Acinetobacter</em> spp. with late onset VAP, MDR: 69.7%, MBL: 30.23%, MBL- 50%</td>
</tr>
<tr>
<td></td>
<td>(10 mths)</td>
<td>28 (20%) develope d VAP.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>35</td>
<td>Retrospective cohort study two-year</td>
<td>60</td>
<td>MDR: 13.3% XDR: 68.3%</td>
<td>Higher SAPS II score, increased hospital LOS prior to ICU, MV, Carbapenem use; mortality due to drug-resistant <em>A. baumannii</em> VAP was high; Potentially pandrug resistant:18.3%</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Cross-sectional (18 month)</td>
<td>(56) CARB resistant</td>
<td>VIM and OXA-23 carbapenemases <em>A. baumannii</em> (88.9 %). <em>A. baumannii</em> displayed phenotypic diversity in AMK, GEN, SXT, tobramycin and rifampicin (8 clusters).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>Type of study</td>
<td>Patients (n)</td>
<td>Prevalence-of VAP &amp; MDR-Ab</td>
<td>Risk factors for VAP</td>
<td>Phenotype and genotype</td>
</tr>
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<tr>
<td>8</td>
<td>Review</td>
<td></td>
<td>Gene clusters responsible for this resistance are <em>bla</em>OXA-23-, <em>bla</em>OXA-24/40-, and <em>bla</em>OXA-58-like gene clusters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Cross-sectional</td>
<td>83</td>
<td><em>bla</em>OXA-23 and IS<em>Ab1</em> linked <em>bla</em>OXA-66: high level imipenem resistance; MDR: <em>bla</em>ADC-25, class 1 integron-borne aminoglycoside modifying enzymes, presence of sense mutations in <em>gyrA</em>/<em>parC</em> and involvement of active efflux (with evidence for the presence of <em>adeB</em> efflux gene). MDR: 79.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cohort</td>
<td>72</td>
<td>Carbapenem resistant: 45 MDR- <em>Ab</em>: 75%</td>
<td>AmpC β-lactamase: 44.4% positive; MBLs: 55.6%-carbapenem resistance; Efflux pump: 77.8%; MBLs and AmpC β-lactamase: meropenem resistance</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Cohort (15 month)</td>
<td>23</td>
<td>β-lactams resistant: 19</td>
<td><em>bla</em>OXA-51 gene was found in all isolates, <em>bla</em>OXA-23: 14 and <em>bla</em>TEM-1 in:3</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Cohort (21 months)</td>
<td>120</td>
<td>IMP resistant: 92%</td>
<td><em>A. baumannii</em>- carried <em>bla</em>OXA-23-like gene and <em>bla</em>OXA-24-like. All 101 <em>bla</em>OXA-23-like positive isolates had the IS<em>Ab1</em> insertion sequence, <em>bla</em>OXA-23-like gene for carbapenem resistance</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Cross-sectional (2 years)</td>
<td>100</td>
<td>89% were resistant to tetracycline 35% to Minocycline 25% to doxycycline All isolates were sensitive to tigecycline</td>
<td>Types A (40%), B (30%), C (10%), D (5%) and E (5%). <em>tet A</em> and <em>tet B</em> genes</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Prospective (1 year)</td>
<td>105</td>
<td>VAP 31.7/1000 day</td>
<td>Duration of MV Trauma</td>
<td><em>Acinetobacter</em> spp: 34.28% Mortality: 48.33%</td>
</tr>
<tr>
<td>33</td>
<td>Descriptive</td>
<td>74</td>
<td>MDR: 100%</td>
<td>head trauma and stroke</td>
<td><em>A. baumannii</em> : 21.0%</td>
</tr>
<tr>
<td>36</td>
<td>Muticentric</td>
<td>2,445</td>
<td><em>Acinetobacter</em>: 67.3% Imipenem resistance; MDR: 82%, XDR: 51.1%</td>
<td><em>Acinetobacter</em> spp were the most frequent isolates</td>
<td><em>Acinetobacter</em> spp were the most frequent isolates</td>
</tr>
<tr>
<td>48</td>
<td>Prospective (20 months)</td>
<td>84</td>
<td>VAP rates 6.242/ 1000</td>
<td>Mortality: 61.84%</td>
<td><em>A. baumannii</em>: 37.63% Majority of them were MDR</td>
</tr>
<tr>
<td>49</td>
<td>Prospective (2 yrs)</td>
<td>144</td>
<td>Early-onset VAP: 24.3%; Late-onset VAP: 26.4%</td>
<td><em>Acinetobacter</em> spp was the most common pathogen in VAP</td>
<td></td>
</tr>
</tbody>
</table>
Risk factors for developing MDR-VAP due to *Acinetobacter* spp:
VAP affects just about 30% of intubated mechanically ventilated patients in ICUs worldwide. Advancing age, male gender, trauma, cerebral hemorrhage, impaired consciousness, higher APACHE II scores, higher SAPS II score, increased hospital stay prior to ICU, prolonged duration of MV, supine head position, prior antibiotic therapy, inappropriate antimicrobial therapy, carbapenem use, longer intubation time, reintubation, tracheostomy renal failure COPD, DM, MOF, stress ulcer prophylaxis and low platelet were found to be associated with the risk of MDR-AB. Occurrence of MDR, XDR and pan-resistant *A. baumannii* has been observed in ICU settings. Risk factors associated with the resistance acquisition mainly include injudicious and broad spectrum antibiotic exposure, prolonged stay in the ICUs, mechanical ventilation and drifting from local antibiogram based antibiotic policies. Investigations of several outbreaks of resistant infections have been recognized to direct contact (bacterial flora of moist regions of skin like axilla and groin). The contamination of hands of Health Care Workers (HCW) occurs even after minor contact with colonized patients [13, 28, 16, 17, 18, 19, 21, 29, 31, 30, 34, 32, 45, 35, 47, 27, 46].

### Incidence of VAP and MDR *Acinetobacter*:
Patro *et al* (2018) in their study quoted 35% VAP rate with *Staphylococcus aureus* were common in early-onset VAP and nonfermenters in late-onset VAP with 60.87% were MDR *Acinetobacter* and positive for AmpC β-lactamase and MBL. *Acinetobacter* spp. showed 100% MDR and sensitive to polymyxin B and tigecycline [7]. A study from India quoted VAP rate of 11.9/1000 VDs with MDR-AB (54%) with presence of ESBL, AmpC and carbapenemase genes [6].

<table>
<thead>
<tr>
<th>References</th>
<th>Type of study</th>
<th>Patients (n)</th>
<th>Prevalence-of VAP &amp; MDR-<em>Ab</em></th>
<th>Risk factors for VAP</th>
<th>Phenotype and genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>Cross-sectional</td>
<td>65</td>
<td>Higher APACHE II scores</td>
<td>European clones I to III, Carbapenem-resistant (novel)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Cross-sectional</td>
<td>66</td>
<td><em>Acinetobacter</em>: 26%</td>
<td>MDR: 86.36%</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Review article 8 (2008-2014)</td>
<td>High rate of resistance to all antibiotics</td>
<td>Increase in imipenem and meropenem resistance from 2010-2011 and 2012-2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>systematic review of 41 studies</td>
<td>CRAB: 64.91%; MDR-AB: 58.51%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>IR-MDR <em>A. baumannii</em></td>
<td>55% of <em>A. baumannii</em> isolates were resistant to imipenem, and 74% had a MDR phenotype</td>
<td>Kuwait (42%), Pakistan (100%), Turkey (98%), UAE (76%), and Saudi Arabia (63%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
al (2014) reported 21.875 per 1,000 ventilator days (20%) incidence rate of VAP (Acinetobacter spp. MBL: 30.23%) [46]. John et al reported 14.85% (23.2 VAP episodes per 1000 ventilator days) incidence of VAP (MDR-AB: 48.21%) [45]. Goel et al. quoted MDR-AB (49.09%) were the most common pathogens isolated producing MBLs [22]. Khalid et al reported MDR-ABi associated VAP were 100% resistant to ampicillin/sulbactam, piperacillin, cefuroxime [33]. A study from North India by Banerjee et al. quoted high prevalence of Acinetobacter related Hospital Acquired Pneumonia (HAP) with resistance to imipenem (bla_{IMPF}, bla_{VIM}, bla-NDM-1 and bla_{OXA-23-like} genes) [17]. Pai et al. (2012) VAP was found to be 44.2% of patients. Acinetobacter species were the most resistant pathogens with high mortality [32]. Ghada et al. in their study stated that, all A. baumannii isolates were multidrug resistant and 75% were resistant to carbapenems but were sensitive to colistin (93.2%) (blaOXA-51-like gene, blaOXA-23 like gene, blaOXA-58) [18]. Dey et al reported incidence of VAP was found to be 45.4% among the mechanically ventilated patients with 47.9% MDR-Acinetobacter spp (AmpC β lactamases MBLs) [19]. Thakuria et al. reported 51%VAP rate with A. baumannii were carbapenemase producers [20]. A study from North India, quoted A. baumanii in 20.9% with VAP. The incidence of VAP in Indian ICUs is ranged from 30% to 73%. Compared to Western data, Gram negative organisms are the most common etiological agents in both early and late VAP in India [51]. Kumari et al reported VAP rate of 13% with predominance of Gram negative organisms including Acinetobacter spp. (13, 21%) [42]. Shaik et al. quoted that, the late onset VAP (60.8%) predominated by Gram negative Bacteria (MDR-AB: 32.1%) [40]. Mathai et al reported VAP rate of 38% (40.1 VAP infections/1000 ventilation days) predominantly caused by GNB (Acinetobacter species: 53.2%) with 27.3% of isolates demonstrated multidrug resistance [30]. Asir et al reported Incidence of VAP 15.2/1000 ventilator days (A. baumannii: 100%) [43]. Karampatakis et al. (2017) stated that, OXA-type carbapenemases are present with highest prevalence worldwide of them bla OXA-23-like, bla OXA-58-like and VIM are the most important genes found in Greece [23]. Ganjo et al. (2016) (Iraq) reported 100% of A. baumannii isolates had blaOXA-51-like genes (blaOXA-51-like gene, blaOXA-23-like gene, blaOXA-58) genes VIM and IMP MBLs blaOXA-58-like upstream ISAba1 insertion) [25]. Ghosh et al. (2018) (India) quoted VAP rate of 6.242/ 1000 ventilator days with mortality of 61.84%. A. baumannii (37.63%) was the commonest organism isolated [48]. Doo et al. (2011) in their multicentric study stated that, major bacterial isolates from VAP cases in Asian countries were due to Acinetobacter spp. (MDR: 82% and XDR: 51.1%) [36]. Ranjan et al. (2014) quoted 57.14% (VAP was 31.7/1000 ventilator days) incidence of VAP in their study (Acinetobacter spp: 34.28%) [47]. Aušra et al. (2019) quoted 13.3% MDR, 68.3% XDR and 18.3% potentially pandrug-resistant A. baumannii [35]. Teerawattanapong et al. (Southeast Asia) (2018) in their systematic review of 41 studies found that, a cumulative incidence of HAI caused by A. baumannii in Southeast Asia was substantially higher with carbapenem-resistance (64.91%) [41]. Maryam et al (2016) in their meta-analysis (2016) of Imipenem-resistant MDR A. baumannii observed that, the 55% imipenem
resistance [38]. Moradi et al. in their review article of 87 papers (2008-2014) from Iran observed an increase in antimicrobial resistance in MDR-AB isolates [50]. Mathai et al. (2012) late-onset VAP developed in 76.85% due to Acinetobacter (MDR-AB: 70%) [28]. A study from India stated that the production of AmpC β-lactamases and MBLs were responsible for the MDR Acinetobacter spp and associated with late-onset VAP (MBL: 20% and AmpC β-lactamases: 60.7%) [16], Ahmed et al. in their study, isolated 80.8% MDR Acinetobacter with Imipenem-resistant (MBL producers blaVIM2) [14]. De et al. (2018) quoted 40.8% incidence of VAP (late-onset VAP: 81.13%) caused by MDR-Acinetobacter spp (70.37%) and were carbapenem resistant [21]. Khelghi et al. (2017) reported 27.5% of patients to have VAP (Acinetobacter spp. 37.83%) producing MBL and AmpC β-lactamases. ICU infections are important cause of mortality and morbidity. Globally Gram positive organisms are prevalent in ICUs, whereas Indian ICUs are overwhelmed with Gram negative organisms including MDR-Acinetobacter spp [15]. Acinetobacter are among the most notorious bacteria isolated in hospital infections, particularly in developing countries. Combined therapy has been an alternative for multi-drug-resistant Acinetobacter. Tigecycline and colistin can be valuable therapeutic options for the treatment of MDR-Acinetobacter infections [52]. Treatment options are limited; carbapenems and colistin are the current agents of choice for the most drug-resistant infections [8]. Upcoming promising drug strategies are new β-lactamase inhibitors, Inhibitors of aminoglycoside-modifying enzymes and multidrug efflux pumps, ukaryotic antimicrobial peptides. To manage patients with VAP comprehensively, requires a multi-disciplinary team effort and approach of clinical microbiologists, physicians and hospital infection control associate.

**Conclusion:**

Multi-drug, extended-drug or pan-drug resistance makes treatment a real medical challenge in MDR-VAP due to Acinetobacter. Inadequate infection control facilities and policies, lack of resources, ignorance for preventive strategy are the main reasons for the rise of MDR organisms in ICU settings. The periodic active surveillance of the ICU environment including the ventilator circuits, respiratory therapist may cut down the significant proportion of ventilator associated pneumonia. There is pressing need to implement an antimicrobial stewardship program supported by the local microbial data integrated with international guidelines to optimize the antimicrobial use may improve outcomes in patients with VAP due to MDR-Acinetobacter. The genotype blaOXA-23-like and blaOXA-51-like genes are the most prevalent genotype in various studies. The a surveillance program of ICU acquired infections, antibiotic usage and molecular typing of MDR A. baumannii isolates may help for making hospital antibiotic policies. The empirical therapy should be broadened (anti-pseudomonal cephalosporin, carbapenem, or β-lactamase inhibitor plus fluoroquinolone, or aminoglycoside plus linezolid) to cover the most probable pathogens including MDR. Tigecycline and colistin should be reserved for resistant cases. Mortality in VAP cases is high due to the increasing incidence of multidrug-resistant organisms in ICUs. Various studies emphasized on
appropriate use of antimicrobial therapy to fight against these MDR-\textit{Acinetobacter} pathogens.

**Key Message:**
Judicious use of antimicrobials, rotational antibiotic therapy, novel preventive, treatment strategies, antibiotic recycling, combinations of antibiotic and development of novel antimicrobial agents will be beneficial to fight against MDR-AB causing ventilator associated pneumonia at large. Early and correct diagnosis of VAP is a challenge for choosing an optimal antibiotic treatment and cure.

**References**


